

REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, claims 18-23, 32 and 34-44 are pending. Claims 1-17, 24-31, 33 and 45-49 are canceled without disclaimer or prejudice to renewal.

Claims 18, 32, 40 and 42 are amended to set forth that the first and second oligonucleotides are single-stranded over their full-length. Support is found, for example, on page 1, lines 27-28, in Example 3 on page 12, line 23 through page 13, line 21, and in Example 5 on page 14, line 17 through page 15, line 13.

Rejection under 35 U.S.C. § 112, new matter

The Examiner has rejected claims 20-23, 35, 37-39, 41, 43 and 45-49 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges that the specification does not describe a solution comprising 3 oligonucleotides. *See*, the present Official Action at page 2. To the extent that this rejection applies to the pending claims, this rejection is respectfully traversed.

The Examiner is respectfully directed to page 8, lines 12-32 (paragraphs 0049-0051 of the published application). Paragraph 0049 (page 8, lines 12-17) expressly teaches that the hybridization may take place in solution (*see*, page 8, lines 12-13). Paragraph 0051 when read in context refers back to paragraph 0049. Paragraph 0051 expressly teaches that the first oligonucleotide and the third oligonucleotide are each labeled with at least one corresponding member of a FRET pair consisting of a FRET donor entity and a FRET acceptor entity. This is the language set forth in claims 20, 35 and 41.

Therefore, no new matter was added by the amendments in the previous response. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

Rejection under 35 U.S.C. § 102(e), U.S. Patent No. 7,081,336 ("Bao")

The Examiner has rejected claims 18, 19, 22 and 43 under 35 U.S.C. § 102(e) as allegedly anticipated by Bao. To the extent that this rejection applies to the amended claims, it is respectfully traversed.

Claim 18 has been amended solely in the interest of furthering prosecution and not out of acquiescence to or agreement with the Examiner. Amended claim 18 sets forth that the first and second oligonucleotides are single-stranded over their full length. In contrast, Bao discloses oligonucleotides that form a stem-loop structure. The Examiner appears to agree that Bao does not disclose or suggest first and second oligonucleotides that are single-stranded over their full length. *See*, page 4 of the present Official Action.

Because Bao does not disclose or suggest each and every element of the claimed invention, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a), Bao in view of U.S. Patent No. 5,866,336 ("Nazarenko")

The Examiner has rejected claim 23 under 35 U.S.C. § 103(a) as allegedly rendered obvious by Bao in view of Nazarenko. To the extent that this rejection applies to the amended claims, it is respectfully traversed.

Claim 23 depends from claims 18 and 20 and therefore contains all of the limitations of the claims from which it depends. Therefore, if claims 18 and 20 are not obvious over Bao in view of Nazarenko, claim 23 is also not obvious.

Regardless, Bao does not disclose or suggest a solution comprising first and second oligonucleotides that are single-stranded over their full length. Nazarenko does not supply the missing elements of Bao with respect to claims 18 and 23. Further, Bao and Nazarenko do not disclose or suggest a solution comprising first, second and third oligonucleotides wherein the first and third oligonucleotides are each labeled with one corresponding member of a FRET pair, as set forth in claims 20 and 23.

Because Bao and Nazarenko do not disclose or suggest all of the elements of claim 23, their combined disclosures do not render the invention of claim 23 obvious. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a), Bao in view of U.S. Patent No. 6,635,427 (“Wittwer”)

The Examiner has rejected claims 32 and 34 under 35 U.S.C. § 103(a) as allegedly obvious over Bao in view of Wittwer.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. *See also, In re Rouffet*, 47 USPQ2d 1453. The court in *Rouffet* stated that “even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination.” *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be “clear and particular.” *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999). Further, in formulating a rejection under 35 U.S.C. § 103(a), the proposed modification cannot render a primary reference unsatisfactory for its intended purpose or change the principle of operation of a primary reference. MPEP§2143.01(V-VI). Also, the Examiner must avoid using impermissible hindsight reconstruction by applying information gleaned only from Applicant’s disclosure. MPEP§2141(II)(C) and 2145(X)(A).

Here, the combined disclosures of Bao and Wittwer do not disclose or suggest all of the elements of the claimed invention, there is no suggestion or motivation to combine Bao with Wittwer, and there is no reasonable expectation of success by combining Bao with Wittwer.

All Claim Elements not Taught

The combined disclosures of Bao and Wittwer do not disclose or suggest first and second oligonucleotides that are single-stranded over their full length and comprise a FRET pair. Bao discloses dual nucleic acid probes that are not single-stranded over their full length, but instead require a hairpin stem-loop. In fact, Bao teaches against using linear oligonucleotides. *See, for example*, column 30, line 56 through column 31, line 36 of Bao.

Wittwer discloses one single-labeled polynucleotide with a fluorescent label attached to a terminal nucleotide. Wittwer does not disclose a second polynucleotide labeled with a member of a FRET pair. To the contrary, to the extent that Wittwer discloses using a second polynucleotide, its label is such the second fluorescent emission signal is independent of the fluorescent emission signal of the first polynucleotide. *See, for example*, claim 35 at column 47, lines 19-35 of Wittwer. Wittwer also expressly teaches away from oligonucleotide pairs labeled with FRET pairs. *See, for example*, column 2, lines 1-19 of Wittwer.

At most, the combined disclosures of Bao and Wittwer disclose a first single-labeled polynucleotide, and a second polynucleotide that must be a hairpin stem loop, wherein the first and second polynucleotides comprise labels that do not form a FRET pair. This is not the invention of claims 32 and 34.

No Suggestion or Motivation to Combine

Applicants respectfully assert that there exists no suggestion or motivation to combine Bao with Wittwer. To the contrary, the compositions disclosed by Bao absolutely require hairpin stem-loop oligonucleotides. Bao expressly teaches away from using single-stranded or linear oligonucleotides at length by stating that the hairpin oligonucleotides have improved specificity and stability over linear oligonucleotides. *See*, column 30, line 56 through column 31, line 36 of Bao.

In attempting to formulate an obviousness rejection by combining the disclosures of Bao and Wittwer by replacing a hairpin stem-loop oligonucleotide of Bao with the linear single-labeled polynucleotide of Wittwer, the Examiner is improperly changing the principle of

operation of Bao, the primary reference. Furthermore, based on the disclosures of Bao, those of skill in the art would be dissuaded from using a linear rather than a hairpin stem-loop oligonucleotide. In view of Bao, those of skill in the art would certainly be disinclined from replacing one of the hairpin stem-loop oligonucleotides of the dual nucleotide FRET pairs described by Bao with a linear single-labeled polynucleotide that is not intended as part of a FRET pair described by Wittwer.

Moreover, Wittwer teaches against using labeled polynucleotides with labels that comprise FRET pairs. *See*, column 2, lines 1-19 and claim 35 of Wittwer. Based on the disclosure of Wittwer, those of skill in the art would understand that the single-labeled polynucleotides described in Wittwer should not be used as a member of a FRET pair. Wittwer also appears to teach away from using dual oligonucleotides labeled with members of a FRET pair generally.

Accordingly, the Examiner's proposed combination changes the principle mode of operation of Bao, the primary reference. Absent impermissible hindsight reconstruction, there exists no suggestion or motivation to combine the disclosures of Bao and Wittwer.

No Reasonable Expectation of Success

The Examiner's proposal of changing the principle mode of operation of Bao by introducing a linear single-labeled polynucleotide of Wittwer would leave the skilled person believing that there was no reasonable expectation of success by replacing a hairpin stem-loop oligonucleotide with a label that is a member of a FRET pair with a linear single-labeled polynucleotide with a label that is not intended to be a member of a FRET pair.

Therefore, the combined disclosures of Bao and Wittwer do not render claims 32 and 34 obvious. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a), Bao in view of Wittwer and U.S. Patent No. 5,437,977
("Segev")

The Examiner has rejected claim 42 under 35 U.S.C. § 103(a) as allegedly obvious over Bao in view of Wittwer and Segev. This rejection is respectfully traversed for the reasons discussed above. Segev does not cure the deficiencies of Bao and Wittwer and there is further no motivation or suggestion to combine Segev with Bao and Wittwer.

The Examiner cited Segev for disclosing a solid support. However, Segev also requires that the primary oligonucleotide probe bind to a bridging nucleic acid molecule. *See*, abstract and claim 1 of Segev. The Examiner's proposed combination of the disclosure of Segev onto Bao and Wittwer adds another level of complexity that does not necessarily improve upon the disclosures of Bao and Wittwer, nor does it result in disclosing or suggesting all of the elements of claim 40.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a), Bao in view of Segev

The Examiner has rejected claim 40 under 35 U.S.C. § 103(a) as allegedly obvious over Bao in view of Segev. This rejection is respectfully traversed for the reasons discussed above. Segev does not cure the deficiencies of Bao and there is further no motivation or suggestion to combine Segev with Bao for the reasons discussed above. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

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Examining Group 1634

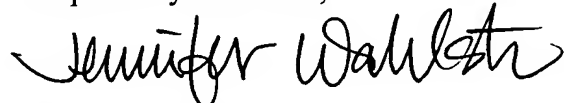
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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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